REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Claims 1-30 were pending in this application and were subject to a restriction requirement. Claims 1-6, 9, 10, 19 and 20 were withdrawn by the Examiner as being directed to a non-elected invention. Claims 1-6, 9, 10, 19 and 20 were cancelled in order to expedite the prosecution of this application. The Applicants reserve the right to pursue the cancelled claims in a future divisional application. Claims 7, 8, 28, and 29 were amended to further clarify the invention and to correct for informalities in the language. Support for this amendment can be found in original claim 7. Accordingly, no new matter has been introduced into the application as a result of the present amendment. Claims 7, 8, 11-18, and 21-30 are now pending in this application.

Turning to the Office action, claims 7, 8, 11-18, and 21-30 stand rejected under 35 U.S.C section 112, second paragraph, for alleged indefiniteness. Claim 7 was amended to correct for typographical errors and to further clarify the invention. Accordingly, the section 112, second paragraph, rejection is moot.

Claims 7, 8, 11-18, and 21-30 also stand rejected under 35 U.S.C. section 103(a) as being allegedly unpatentable over Moon et al. (U.S. Patent No. 5,273,975)("Moon") in view of Gioco et al. (U.S. Patent No. 5,565,466)("Gioco"). The Examiner alleged that Moon teaches a genus of compounds that encompasses the elected compound in a dosage range of 10 to 1200 mgs per day in multiple doses, that the compounds can be administered orally, and that pharmaceutical acceptable salts such as malate can be employed. The Examiner admits, however, that Moon does not expressly teach the elected compound (5R)-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-I]quinolin-2(1H)-thione. The Examiner further alleged that Gioco teaches a method of modulating the excitory phase of female sexual response using vasodilating agents such as phentolamine. On this basis, the Examiner asserted that it would have been obvious to an ordinary skilled artisan to orally administer (5R)-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-thione to increase sexual desire, interest or performance in humans and further to employ a secondary agent based on Moon's alleged disclosure of compounds, dosage ranges, and CNS-based conditions, to stimulate sexual behavior and Gioco's

alleged disclosure of modulating female sexual response using vasodilating agents such as phentolamine. Applicants respectfully traverse this rejection.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit emphasized by succinctly summarizing: "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicants' disclosure." *Id.* Contrary to the Examiner's position, neither Moon nor Gioco, alone or in combination, suggest doing what the Applicants have done.

(a) Moon does not teach or suggest the presently claimed utility

With regard to utility, Moon disclosed at column 2 at lines 19-23:

> In addition, central 5-HT receptor activation are believed to be involved in mediating sexual behavior. These compounds would be useful to stimulate sexual activity and to alleviate impotence.

Moreover, Moon taught that his compounds should be used in a dosage range of 10 mg to 1,200 mg (column 9, lines 58-65). While the application of Moon to support a section 103 rejection may appear be reasonable, the appearance is illusory, especially in light of Dr. Meglasson's Declaration discussed below.

Dr. Meglasson's Declaration describes the clinical evaluation of Applicant's (5R)-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-I]quinolin-2(1H)-thione ("elected compound") and its structural analog, (5R)-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one ("analog compound"). Neither one of these compounds have been specifically exemplified in Moon.

The analog compound (in salt form) is in human clinical phase II/III trials for treatment of Parkinson Disease. The analog and elected compounds have been tested in human clinical trials for human sexual dysfunction.

As stated by the Examiner, in view of Moon's teachings, one skilled in the art would believe that the elected compound would be useful for the claimed method in the dose range taught by Moon. However, surprisingly and unexpectedly, that is not the situation. Given the teachings of Moon, the facts of the actual situation are indeed surprising and unexpected. The facts and the reason why the claims (as amended) are nonobvious in view of Moon are set forth in Dr. Meglasson's Declaration and summarized below:

(1) neither the analog compound nor the elected compound was exemplified in Moon.

(2) when used in treating Parkinson's Disease, the analog compound is administered as the salt in a dosage range of about 8 mg/day to about 48 mg/day which is substantially within Moon's disclosed range of 10-1,200 mg/day.

(3) clinical trials in normal volunteers and patients with sexual dysfunction with the analog compound and the elected compound have shown:

(a) Both the analog compound and the elected compound are not tolerated above 5 mg/day because of orthostatic hypotensin, vomiting, nausea and dizziness.

(b) Both the analog compound and the elected compound would not be useful at 10 mg/day and above[1]. The dose is in μg/kg. Hence, the:

0 μg/kg is equivalent to 0 mg/70 kg (control),

20 μg/kg dose is equivalent to 1.4 mg/70 kg,

50 μg/kg is equivalent to 3.5 mg/70 kg and

125 μg/kg is equivalent to about 9 mg/70 kg. The data clearly show that the 9 mg dose is the same as the control whereas the 1.4 mg and 3.5 mg doses increase sexual activity.

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[1] A brief explanation of why the analog compound is too toxic to use for the claimed method but still can be effectively used at higher doses to treat Parkinson's disease, it is because to treat Parkinson's disease the pharmaceutical agent is given continuously and the side effects disappear whereas with the claimed method the pharmaceutical agent is not taken on a daily basis. See the enclosed Declaration of Dr. Meglasson for a more detailed discussion.

Hence, if one tested the analog compound (or its salt form) or the elected compound in the oral dose range taught by Moon (10 mg to 1,200 mg), the evidence indicates:

(1) there is no utility for the claimed purpose and

(2) there is too much toxicity.

Therefore, Moon does not teach or enable the claimed invention. This is not a case of optimizing a dose within a dose range. Moon's dose range is not operable for the claimed invention. The 10 to 1,200 mg dose range is a broad one and thus would not be considered "a sexually useful effective amount" as presently claimed. The claimed method is not operable anywhere in Moon's range. Therefore, based on the factual data from Dr. Meglasson's Declaration, the effective daily dose range for Moon should be >10mg/day whereas the suitable dosage range is limited to less than that amount.

Further, support for the narrow useful dose range of the present invention comes from the fact that analog compound and the elected compound have a narrow bell shaped curve for producing sexually enhancing effects, see Dr. Meglasson's Declaration, Part III(A). This supports the fact that an optimum dose of 2-5 mg means no activity at about 10 mg.

In addition, the clinical finding related to drug tolerance indicates that there is a big difference between 5 mg and 10 mg.

In summary, Dr. Meglasson's evidence shows:

(1) that the analog compound are useful for treating Parkinson's Disease, a CNS disease, in a dose of from 8-48 mg/kg which is consistent with Moon's disclosed dosage range of from 10-1,200 mg;

(2) that the analog compound and the elected compound are not useful above about 6 mg because of toxicity;

(3) that analog compound and the elected compound are useful for the claimed indication in the dosage range of about 0.5 to 5 mg/day.

Hence, it is clear that Moon does not teach the claimed invention. If anything Moon teaches away (>10 mg/day) from a "sexually useful effective amount" as presently claimed.

This showing of inoperativeness of Moon for the utility disclosed in column 2, lines 21-23 does not in any way impeach or affect the validity of Moon. Dr. Meglasson's Declaration even supports Moon as it relates to the effective dose range for treating Parkinson's Disease (column 2, line 13). The fact that the dosage range disclosed by Moon is not useful or does not enable additional uses is irrelevant to Moon. However, it does show the unobviousness of the claimed invention including a dosage range outside of that disclosed by Moon.

(b) A CNS teaching in Moon is not a teaching or suggestion of the presently claimed invention.

Claim 11 of Moon states the following:

> 11. A method for treating central nervous system disorders in animal or human hosts in need thereof comprising the administration of a pharmaceutically effective amount of a compound of claim 1.

The disclosure of Moon in column 2, lines 21-23 set forth below also states:

> In addition, central 5-HT receptor activation are believed to be involved in mediating sexual behavior. These compounds would be useful to stimulate sexual activity and to alleviate impotence

The disclosure at column 2 of "... useful to stimulate sexual activity..." is much closer to the claimed invention than is the broad general disclosure of claim 11, and therefore since the applicants have shown nonobviousness over the closer disclosure of column 2, "useful to stimulate sexual activity and to alleviate impotence," it is believed that the applicants have established nonobviousness over the disclosure of claim 11 as discussed above.

Moreover, as Dr. Meglasson attests, it is widely believed that many forms of sexual dysfunction do not result from a central nervous system disorder. Indeed, the etiology of sexual dysfunction is complex and multifactorials, but cardiovascular, hormonal, and social relationship factors are widely considered to be the primary causal factors. See Declaration at Part III (D). Accordingly, Moon's disclosure of a method for treating CNS disorders is not a disclosure of treating sexual dysfunction.

(c) Moon's disclosure of "multiple doses" is not a teaching or suggestion of the claimed doses.

In col. 9, lines 58-61, Moon states:

> Initial dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1,200 mg per day orally, which may be given in a single dose or in multiple doses.

It is believed that the Examiner is concerned that Moon includes a multiple of small doses that add to 10 mg and would teach the claimed invention. For example, a 10 mg dose could be given in four 2.5 mg doses and the present invention includes a 2.5 mg dose.

First, four 2.5 mg doses is still 10 mg/day, which is at least twice the limit (5 mg) found to be effective in increasing sexual desire, interest or performance.

Second, Dr. Meglasson's Declaration provides evidence that while multiple doses in a day totaling 10 mg or more is operative for the non-sexual function CNS disorders of Moon (Parkinson's Disease), it is not useful for the claimed invention for increasing sexual desire, interest, or performance. Accordingly, Moon's dosage range is not a disclosure or suggestion of "sexually therapeutic effective amount" as recited in the present claims.

(d) Moon's disclosure of "ED50's values of as low as 0.05 mg/kg" is not a suggestion of the claimed invention.

Moon has a number of disclosures which relate to doses and which appear to be in conflict. The relevant disclosures of Moon relating to doses are as follows:

> (1) "The compounds listed below were tested and found to have possible useful antipsychotic activity properties as indicated by their having CNS activity (ED_{50} numbers of less than 50 mg/kg values) in the known hypothermia and/or hypoxic stress tests;" (Column 9, lines 3-7)

(2) "Doses of the compound under study began at 100 mg/kg and were decreased at a 0.3 log interval until no responders were obtained." (column 9, lines 11-14)

(3) In the hypothermia and hypoxic stress tests, compounds of the invention have been found more potent than related compounds, showing $ED_{50's}$ values as low as 0.05 mg/kg. (column 9, lines 40-43)

(4) That the compounds were dosed intraperitoneally (ip) or subcanteously (sc) when tested in mice (column 9, lines 9-11).

(5) that "the compounds also had good activity in the hypothermia test when the animals were dosed orally with the drug" (column 9, lines 43-45).

(6) That with respect to dosing in humans for the purpose of producing therapeutically beneficial effects "Initial dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1200 mg per day orally;" (column 9, lines 59-60)

As disclosed in the file history of Moon, the Examiner's position was that since the average individual is about 70 kg, the dosage would translate to 3.5 mg ((70 kg)(0.05 mg/kg) = 3.5 mg) and 3.5 mg is in the middle of the dose range (0.5 to 5 mg) of the claimed invention. It also appears that some of the statements conflict with others.

In fact there is absolutely no conflict between the various statements in Moon's dosages because statements (5) and (6) relate to oral administration and statements (1), (2), (3) and (4) related to parenteral administration. Part (II)(C) of Dr. Meglasson's Declaration addresses this apparent problem and provides more than ample evidence there is absolutely no conflict. In summary, Dr. Meglasson asserts that:

(a) while statements (1), (2), (3), (4), and (5) and (6) appear to be in conflict, they are not in conflict;

(b) statements (1), (2), (3), and (4) related to parenteral administration;

(c) statements (5) and (6) relate to oral administration;

(d) the statements are not in conflict because they are related to different things, statements (1), (2), (3), and (4) relate to parenteral administration and statements (5) and (6) relate to oral administration; and

(d) That it is my opinion that statements (1), (2), (3), and (4) are correct with respect to teaching that the compounds of the invention likely possess antipsychotic, and statement (5) is correct with respect to the principle that the compounds can be administered orally, but the foregoing statements are irrelevant to statement (6), which relates to the effective dosage when (1), (2), (3), and (4) do not teach the therapeutic oral dosage of compounds of the invention because these statements related solely to parenteral drug administration. Statement (5) does not teach the therapeutic oral dosage since it does not describe an effective oral dose.

Therefore, the statement that the Examiner believed teach doses within the claimed dose range does not because it refers to parenteral administration and therefore parenteral doses. Hence the relevant statement in Moon regarding oral doses is statement (6) which teaches a dose of "at least 10 mg up to about 1200 mg". Dr. Meglasson's Declaration has more than ample evidence with regard to both compounds of the invention, that doses of 10 mg (Moon) are inoperable for the present invention. Dr. Meglasson testified:

These data indicate that healthy adult men and women tolerate PNU-9566E at a dose of 5 mg, but not at a dose of 10 mg or greater. These data define the operative range for a single oral dose of PNU-9566E as being less than 10 mg and most desirably 5 mg or less to assure patient comfort and safety;

These data indicate that healthy adult men and women tolerate PNU-142774E at a dose of 2 mg, but not at a dose of 4 mg or greater.

In summary, Moon discloses a number of CNS utilities and also "These compounds would be useful to stimulate sexual activity and to alleviate impotence." See column 2, lines 21-23. However, the only oral dose disclosed by Moon is: "Initial

Dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1200 mg per day orally." See column 9, lines 59-60. The applicants by way of Dr. Meglasson's Declaration have provided actual dose evidence that the dose range taught by Moon is fine for treating Parkinson's Disease, but is inoperable for the sexual desire disorder being claimed in the present patent application and thus cannot be considered a "sexually useful effective amount" as presently claimed.

Therefore, there is an amazing situation here where the same agent must be given at a different dose and different frequency of dosing to be effective. Even though a high dose (8 – 48 mg/kg) is operable for CNS by giving too much (more than about 0.5 or 5 mg, for instance), the increase sexual desire effect is lost.

(e) Gioco does not teach or suggest the claimed invention

As discussed above, the primary reference, Moon, does not anticipate or render obvious Applicants' claimed invention. Applicants maintain that the secondary reference, Gioco, either alone or in combination with Moon would not motivate an ordinary skilled article to administer Applicants' compounds of formula A with a second agent. Gioco is completely silent with respect to combining any vasodilating agent with other agents for the purpose of increasing sexual desire, interest or performance.

For all of the above reasons, Applicants respectfully submit that the §103 rejection based on Moon in combination with Gioco against the claims should be withdrawn and that claims 7, 8, and 11-30 are allowable.

Reconsideration of this application and a favorable determination is respectfully requested. The Examiner is invited to contact the undersigned if the Examiner believes that this would be helpful in expediting the prosecution of this application.

Respectfully submitted,

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